



Regulatory Submissions,
Information,
and Document
Management Forum

February 13-15
North Bethesda, MD

#RSIDM23



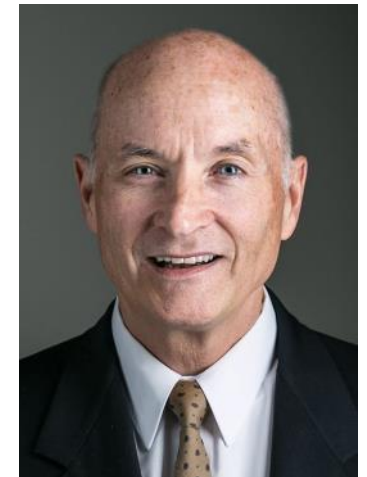
Standardizing Quality Submissions and Assessments: PQ/CMC and KASA

Norman R. Schmuff, Ph.D.

Center for Drug Evaluation and Research

Office of Pharmaceutical Quality

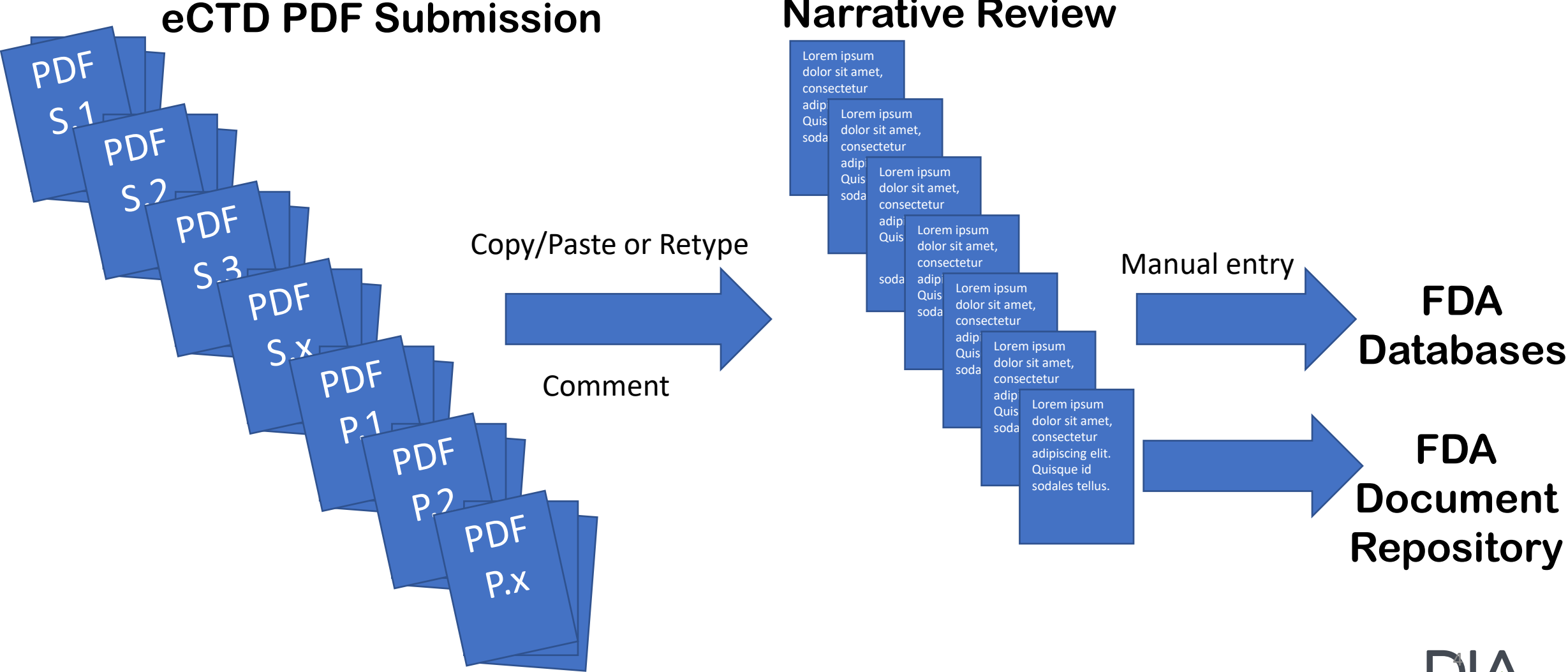
Office of Pharmaceutical Manufacturing Assessment



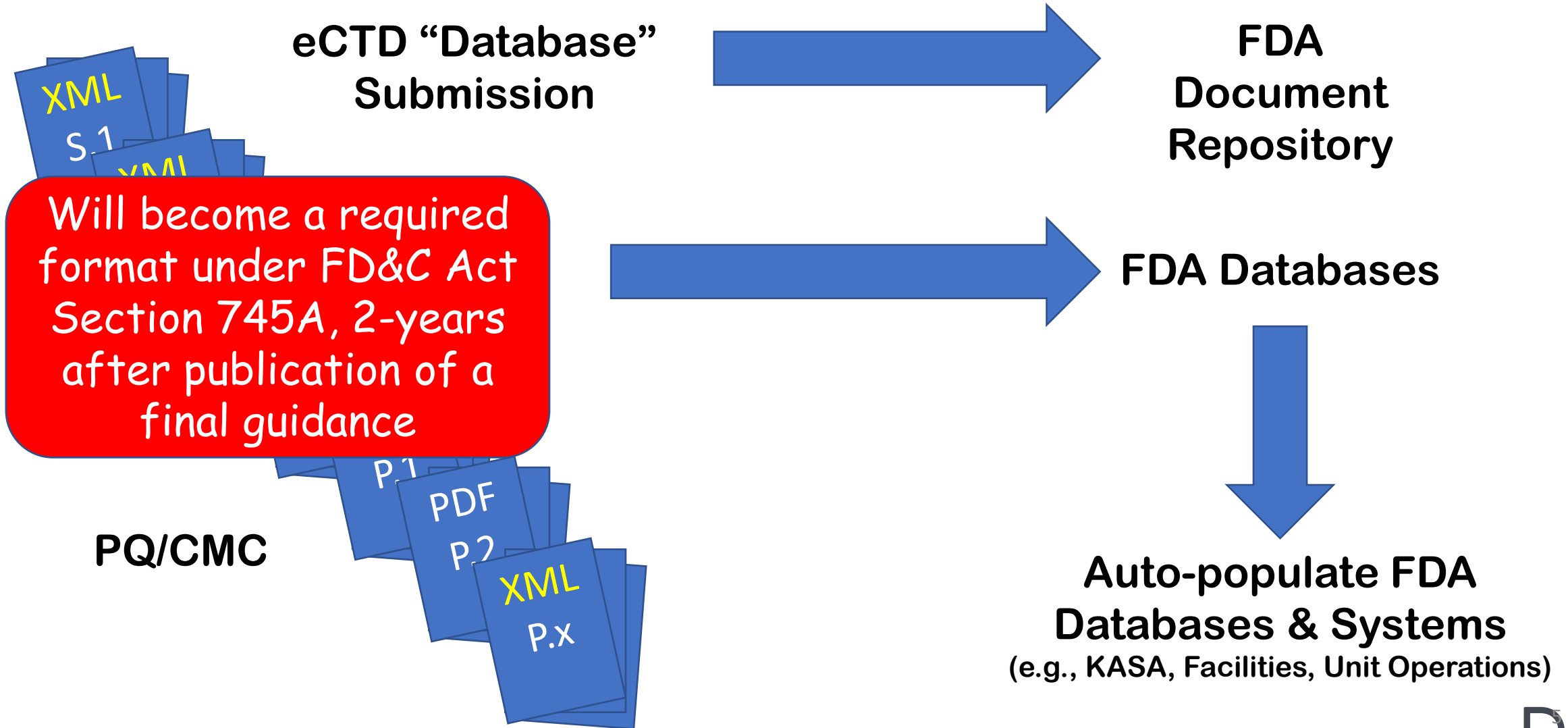
Outline

- Our vision
- What we've done
- ISO Identification of Medicinal Products (IDMP)
- International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)
- Current work
- Challenges
- Preparing for the Future of Structured Submissions

Current Module 3 Submission Model

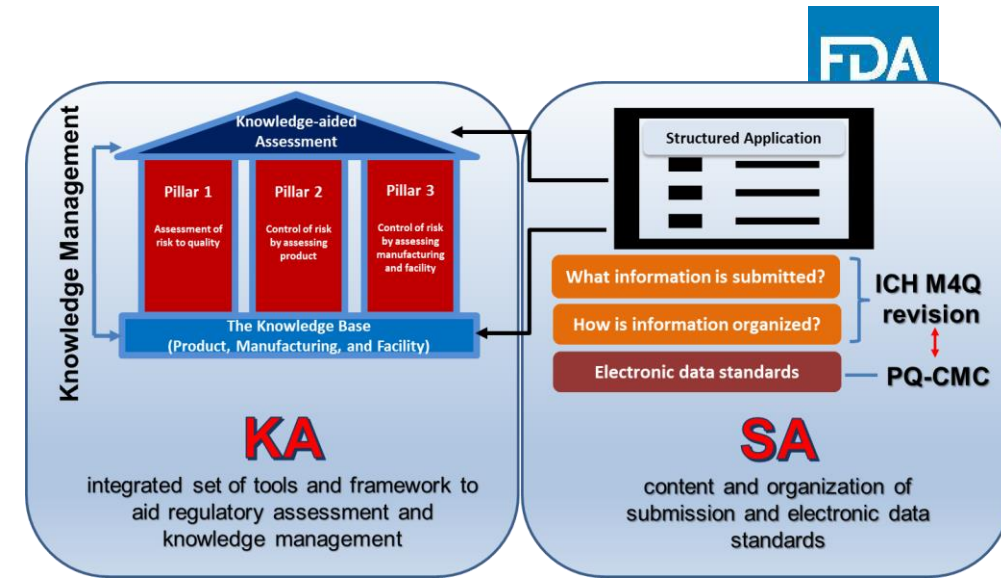


Possible Future Module 3 Submission Model



PQ/CMC and KASA

- PQ/CMC (Pharmaceutical Quality/ Chemistry, Manufacturing, and Controls)
 - Standardize & structured eCTD **submissions**
 - XML, JSON? and HL7 FHIR
 - Controlled vocabularies for drop-down lists
- KASA (Knowledge-Aided Assessment and Structured Application System):
 - Pre-populated structured **assessments**
 - Risk-ranking algorithms
 - Pre-analyzed data, e.g., linear regression of stability data
 - Data analytics
 - Comparison to historical data
 - Lifecycle knowledge management
- Implementation of PQ/CMC will significantly enhance the KASA system, by removing manual (semi-automated) data transposition



What we've done

- Assembled SMEs across CDER, CBER & CVM
- Standardized terminology and definitions
- Modeled specification & components and composition
- Tested proof of Concept with 7 PhRMA firms
- Harmonized data element with the KASA system
- Collaborated with stakeholders and other interested parties e.g.,
 - Health Level 7 (HL7)
 - European Medicines Agency (EMA)

What we've Published

- Federal Register
 - 2017 FR Notice*: Phase 1 PQ/CMC Terms and Definitions
 - Main comments: Our Response
 - Effort should be international: Response (next slide)
 - Terminology should conform to ISO IDMP**: Response
 - Completed a 157-page mapping document
 - Held a collaborative mapping webinar with PhRMA
 - 2022 FR Notice***: PQ/CMC to HL7 FHIR Mapping
 - Comments period closed May 17
 - Received comments from 8 parties

* <http://go.usa.gov/xNe8S>

** Identification of Medicinal Products (5 ISO standards) <http://go.usa.gov/xzuxc>

*** <http://go.usa.gov/xzVdc>

PQ/CMC and ICH

- “Structured Product Quality Submissions” (SPQS) accepted as a topic by the ICH Assembly
- Prioritized as follows:
 - After Q13 completes Step1/Step 2 (Step 2b completed:27 July 2021)
 - New M4-Q (CTD-Q) Expert Working Group in progress with FDA’s Lawrence Yu as Rapporteur
 - SPQS group formation to be determined by new M4-Q EWG
- FDA’s PQ/CMC will continue

Identification of Medicinal Products (IDMP)

- Goal: Define data elements and structures for the unique identification and exchange of medicinal product information
- Five standards:
 - Substances (ISO 11238)
 - Pharmaceutical dose forms, units of presentation, routes of administration and packaging (ISO 11239)
 - Units of measurement (ISO 11240)
 - Regulated pharmaceutical product information (ISO 11616)
 - Regulated medicinal product information (ISO 11615)

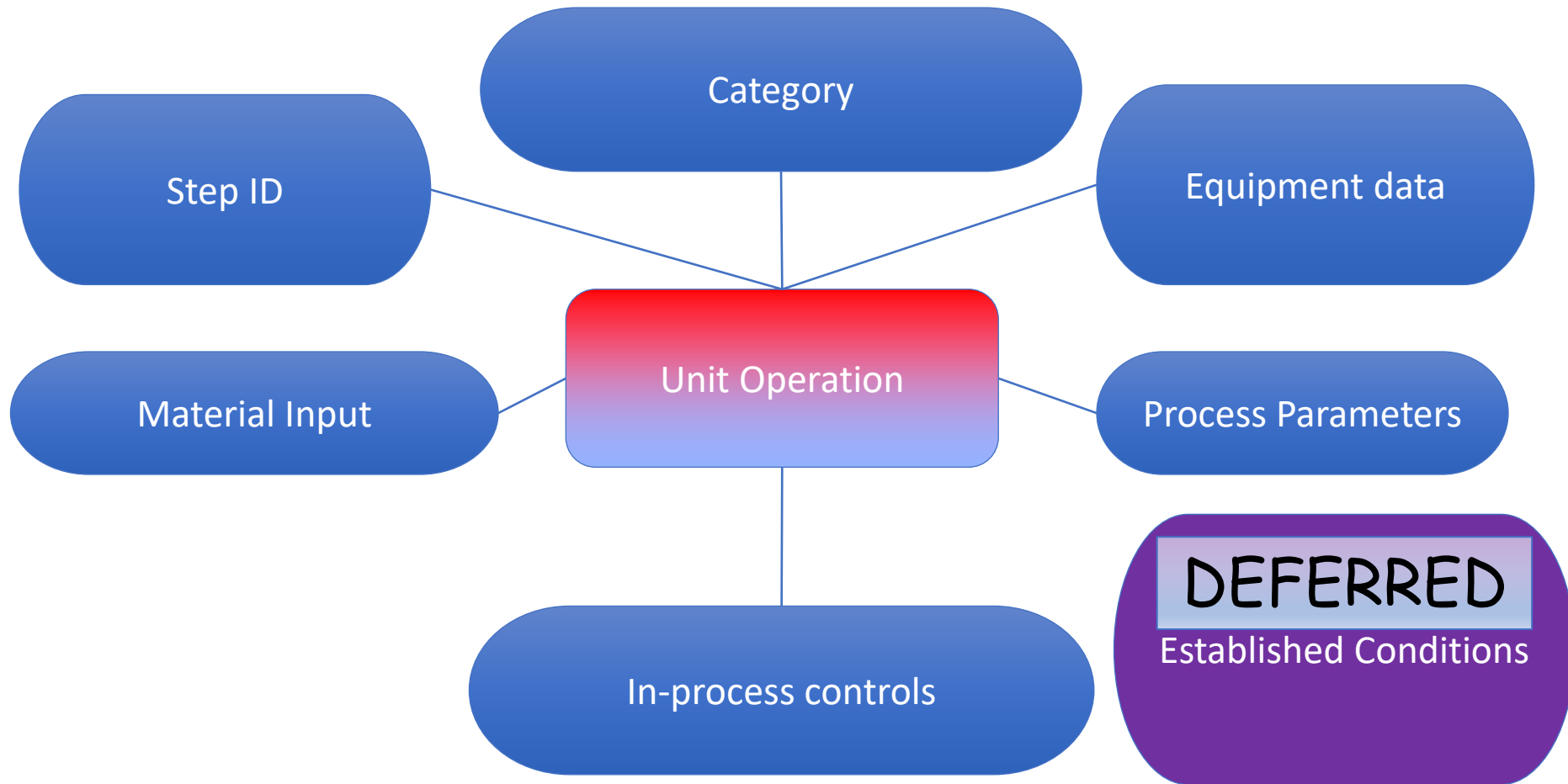
“Terminology should conform to ISO IDMP”

- Mapping is problematic, e.g., different granularity
- Many code lists are deferred to regional implementation (e.g., MPID)
- Some terms are regionally mandated (e.g., US FD&C statute, USP requirements)
- Some regions have multiple code lists used in different contexts, e.g., FDA has four dosage form lists in use
 - USP terminology is required by FD&C Act in labeling
 - SPL uses a list from the NCI Enterprise Vocabulary Service
 - Orange book uses a list for acceptable ANDA submissions
 - ICH allows for the EDQM list as an option for E2B submissions
- PQ/CMC terminology will be aligned with where possible, but conformance frequently not feasible

Standardized Terminology & Definitions

- Why
 - Eliminates confusion about synonyms, potentially synonymous terms
 - Enables an ontology (i.e., properties and the relations between them)
 - Permits data analytics
(e.g., how many assay procedures use CZE, for what classes of drugs)
 - Facilitates risk-ranking
- Controlled vocabularies (ISO: coded concepts)
 - Enables drop-down lists & data analytics
 - E.g., “Ingredient role” for PQ/CMC (Active, Inactive, Adjuvant)

Drug Product Unit Operations



- * From 2014 “SUPAC: Manufacturing Equipment Addendum Guidance for Industry”
- # For manufactured exhibit lots
- ^ Controlled vocabulary code list

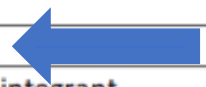
Typical WG Meeting Activity

PQ/CMC - KASA - Trk 2 meeting - 8/6/2021 --Harmonization Notes for Excipient Function Names

#	KASA Excipient Function List	PQ/CMC Excipient Function Names Mapping to KASA list	NEW values to be added to PQ/CMC Excipient Function Names List	Recommendations/ Notes for KASA & PQ/CMC
1	API	NA		
2	Acidifier	pH Modifier		
3	Adhesive	Adhesive		
4	Alkalizing Agent	pH Modifier		
5	Anti-Adherent	Lubricant		
6	Anti-foaming Agent	GAP	NEW - Anti-foaming Agent	<div style="border: 2px solid black; background-color: #00AEEF; padding: 10px;"> <p>Notes here on harmonization of:</p> <ul style="list-style-type: none"> • Consensus terminology • Who will make the change </div>
7	Antioxidant	Antioxidant		
8	Anti-static Agent	GAP	NEW- Anti-static Agent	
9	Anti-tacking Agent	Lubricant		
10	Binder	Binder		
11	Buffer	Buffering agent		
12	Chelating Agent	Chelating agent		
13	Colorant	Organoleptic agent		
14	Crystallization inhibitor	GAP	NEW- Crystallization inhibitor	
15	Cushioning agent	Filler		
16	Diluent/Filler	??		
17	Disintegrant	Disintegrant		
18	Emulsifier	Emulsifying Excipient		

Notes here on harmonization of:

- Consensus terminology
- Who will make the change



What we plan to do



- Continue external collaboration
 - International Pharmaceutical Regulators Programme (IPRP)
 - ICH M4Q
 - UNICOM
 - EMA
 - HL7
 - Industry Partners
 - IRIS IDMP
 - ISO TC215 WG 6 IDMP
 - Global IDMP Working Group (WHO Uppsala)
 - CTADHL
- Continue internal collaboration
 - FDA IDMP Steering Committee
 - FDA Global Substance Registration System (GSRS)
 - FDA Data Standards Board
 - CDER Data Standards and Data Governance Board
 - CDER Product Data Control Board
- Model other Module 3 & 2.3 CTD sections
- Publish a Draft PQ/CMC Guidance (estimated in 2024)

PQ/CMC IDMP Challenges

- In IDMP standards
 - Spun out of ICH initially as a pharmacovigilance topic
 - 11238 SSG 4 specification use case differs from PQ/CMC
 - Not all terms are defined
 - Most controlled vocabulary code (“coded concept”) lists undefined
- PQ/CMC items not included in IDMP
 - Stability
 - Quality data for drug product, e.g., specification (may include test stages)
 - Quality data for excipients
 - Lifecycle model for specification
 - Batch Analysis Tables
 - Control of Excipients

Challenges

- Standards
 - Diversity e.g., IDMP, UNICOM, SPOR, ICH, CFR, EMA, MEDDRA, EDQM
 - Gaps e.g., controlled vocabulary (CV) for analytical procedures, chemical & physical attributes for characterization, specification, in-process controls; IDMP code lists
- Developing data models & ontologies
- HL7
 - Lack of vendor support for product quality related FHIR transport format
 - No PQ/CMC “Resource” results in mapping
- Internal FDA infrastructure

Conclusion

- PQ/CMC will
 - Substantially change the submission process
 - Necessitate new business processes and infrastructure for FDA and applicants
- Years in the future
 - To become a required submission under 745A(a)
 - ICH “Structured Product Quality Submissions”

Preparing for the Structured Data Future

- Follow PQ/CMC, ISO IDMP, SPOR Developments (with e.g., Google alerts)
- Collect & organize your data in line with IDMP, PQ/CMC & EMA's SPOR
 - Apply “Master Data” concepts
 - Group data according to IDMP concepts
 - Drug Substance
 - Drug Product (e.g., regional MPIDs* for all marketing regions)
 - Dosage form (e.g., consider adding an administrable dose form used in PhPID**)
- Do data cleansing, QC, curation

* MPID: **Regional** Medicinal Product Identifier with three standardized segments described in ISO 11615

** PhPID: **Global** Unique Pharmaceutical Product Identifier, currently an MD5 algorithmically generated 32-digit hash code as described in ISO TS 20415